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| 09/463,590 | 04/20/2000 | SAMUEL J. LANDRY | 07005/00302 | 6521 |

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| EXAMINER | |
|---|---|
| DIBRINO, MARIANNE NMN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

DATE MAILED: 09/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/463,590 | LANDRY, SAMUEL J. | |
| | Examiner | Art Unit | |
| | DiBrino Marianne | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-8,10-13 and 15-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-13 and 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *attached hereto* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Prosecution in this case is HEREBY REOPENED.

2. Applicant's amendment filed 5/17/04 is acknowledged and has been entered.

3. With regard to Applicant's comments on page 6 of the said amendment with regard to the telephonic interview on April 23, 2004, that language that clearly delineated the differences between instant claim 1 and the prior art was agreed upon, the Examiner points out that the Examiner did not agree that the proposed claim language would overcome the prior art of record, but agreed to give the matter further consideration.

4. Claims 1-8, 10-13 and 15-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed lipopeptide and vaccine thereof, recited in the instant claims.

The instant claims encompass a method for stimulating an immune response specific toward a naturally-occurring protein in an animal having an immune system including T cells, said method comprising administering to the said animal an altered protein or polypeptide fragment thereof derived from said naturally occurring protein wherein an unstable polypeptide segment has been inserted by artifice into the interior of the primary amino acid sequence of said naturally occurring protein, wherein the said unstable polypeptide segment conforms to recited limitations in instant claim 1, and wherein the administration is to prevent infection or to inhibit growth of a neoplastic cell in vivo or as a vaccine. There is insufficient disclosure in the specification on such a method.

The specification discloses that local instability within a protein directs immunodominance and enhances susceptibility to proteolytic attack for preferential presentation of adjacent peptides (page 27 at lines 14-18). The specification further discloses that presentation appears to be biased toward presentation of the sequence on the C-terminal side of an unstable segment (page 32 at lines 5-7). The specification discloses that the sites for insertion of flexible loops should comprise the following: that the site should lie on the N-terminal side of a sequence that has characteristics of a

good T cell epitope, the target cell epitope should be among epitopes primed in infections in the case of a protein from an infectious agent, the site should not be located in a known neutralizing antibody epitope nor in a sequence where mutations are known to disturb a neutralizing antibody epitope (paragraph spanning pages 42 and 43), and the insertion site is in a sequence predicted to form a turn or make a structural transition to allow the loop to be exposed while causing the least disturbance to the protein structure (page 43 at lines 9-13).

The specification does not disclose using an altered protein or polypeptide fragment thereof, including said fragment not possessing a T cell epitope and/or the unstable polypeptide segment, as recited in the instant claims to prevent an infection, to inhibit the growth of a neoplastic cell or to use as a vaccine in vivo.

The instant disclosure does not adequately describe the scope of the claimed genus. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

5. Claims 1-8, 10-13 and 15-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the instant invention, a method for stimulating an immune response comprising administering an altered peptide or fragment thereof containing an unstable polypeptide fragment as recited in the instant claims. The specification has not enabled the breadth of the claimed invention because the claims encompass a method for stimulating an immune response specific toward a naturally, protein in an animal having an immune system including T cells, said method comprising administering to the said animal an altered protein or polypeptide fragment thereof derived from said naturally occurring protein wherein an unstable polypeptide segment has been inserted by artifice into the interior of the primary amino acid sequence of said naturally occurring protein, wherein the said unstable polypeptide segment conforms to recited limitations in instant claim 1, and wherein the administration is to prevent infection or to inhibit growth of a neoplastic cell in vivo or is used as a vaccine. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed method can used prophylactically as a vaccine, including to prevent infection, or can be used to inhibit growth of neoplastic cells in vivo, including wherein the altered protein or polypeptide fragment thereof has inserted therein an unstable polypeptide fragment anywhere in the primary sequence of the naturally occurring protein and wherein proteolytic cleavage may be directed to areas where no epitopes for T cells exist, and including wherein the poplypeptide fragment thereof does not contain a T cell epitope and/or an unstable polypeptide segment or wherein the structure of the fragment is altered so as to change the

secondary/tertiary structures. The specification discloses no working examples with regards to the use of the instant invention for prophylactic/vaccine use, or inhibition of neoplastic cell growth in vivo. In addition, the specification does not disclose how to practice the claimed method wherein the C-terminal portion of the unstable polypeptide segment overlaps the N-terminal portion of the T cell epitope.
The specification discloses that local instability within a protein directs immunodominance and enhances susceptibility to proteolytic attack for preferential presentation of adjacent peptides (page 27 at lines 14-18). The specification further discloses that presentation appears to be biased toward presentation of the sequence on the C-terminal side of an unstable segment (page 32 at lines 5-7). The specification discloses that the sites for insertion of flexible loops should comprise the following: that the site should lie on the N-terminal side of a sequence that has characteristics of a good T cell epitope, the target cell epitope should be among epitopes primed in infections in the case of a protein from an infectious agent, the site should not be located in a known neutralizing antibody epitope nor in a sequence where mutations are known to disturb a neutralizing antibody epitope (paragraph spanning pages 42 and 43), and the insertion site is in a sequence predicted to form a turn or make a structural transition to allow the loop to be exposed while causing the least disturbance to the protein structure (page 43 at lines 9-13).

Evidentiary reference the Merck Manual teaches that a vaccine is a suspension of whole or fractionated bacteria or viruses that have been rendered nonpathogenic and is given to induce an immune response and prevent subsequent disease.

Evidentiary reference Encyclopedia Brittanica Online defines vaccine as a suspension of weakened, killed, or fragmented microorganisms or toxins or of antibodies or lymphocytes that is administered primarily to prevent disease.

Evidentiary reference Chaux et al (Int. J. Cancer. 1998, 77: 538-542) teach that the induction of an immune response does not always necessarily correlate with tumor cell regression or inhibition of growth, and that very sensitive assays are required for detection of CTL response towards some tumor specific antigens.

Evidentiary reference Hsiao et al (J. Immunol. 2004, 172: 1508-1514) teach that many tumor cells produce TBF-β1 which allows them to evade CTL-mediated immune responses, evidentiary reference Anicnini et al (J. Exp. Med. 1999, 190(5): 651-667) teach the absence of tumor regression in patients with an expanded peripheral T cell pool to Melan-A/Mart-1 tumor antigens, and evidentiary reference Ladanyi teaches that the presence of tumor-reactive CTL in the circulation or in the tumors does not guarantee an efficient immune response, i.e., tumor regression ("inhibit growth" recited in instant claim 5).

There is insufficient guidance in the specification as to how to make and/or use the instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is indefinite in the recitation of "wherein the C-terminal portion of said unstable polypeptide segment overlaps the N-terminal portion of said T cell epitope because it is not clear what is meant.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-8, 10-13 and 15, 16, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vitiello et al (J. Clin. Invest. 1995 ,95: 341-349) in view of Rogers et al (Science 1986, 234(4774) : 364-368), Gilbert et al (Nature Biotechn. 1997, 15: 1280-1284), So et al (J. Biol. Chem. 1997, 272(51): 32136-32140) and Novotny et al (FEB, 1987 211(2): 185-189, IDS reference).

Vitiello et al teach that most recombinant proteins and CTL peptide epitopes are poor immunogens with regard to eliciting a class I restricted CTL response, so modification by attaching a T helper peptide (HTL) epitope such as tetanus toxoid peptide 830-843 and two lipid molecules such as palmitic acid improves immunogenicity and results in long-term memory CTL induction (especially abstract and Figure 1). Vitiello et al teach that the structure of the lipopeptide is 2 molecules of palmitic acid coupled via a KSS linker, i.e., comprising a linkage of a charged amino acid residue, to the tetanus toxoid 830-843 T promiscuous, i.e, multivalent, auxiliary epitope linked via a AAA linker to HBV core 18-27 CTL peptide epitope (especially Figure 1). Vitiello et al teach that lipid modification of antigenic peptides enhances their immunogenicity (especially paragraph spanning columns 1 and 2 on page 347). Vitiello et al teach that lipid modification of peptides may help them translocate across the plasma membrane into the cytoplasm, leads to the persistence of peptides at the site of injection or in the draining lymph node for sufficient time to induce a CTL response (ibid). Vitiello et al teach that the CTL epitope must be cleaved from the remainder of the lipopeptide in

order for it to associate with MHC class I molecules, and that the lipopeptide is 1000-fold less efficient in sensitizing targets for lysis by CTL than the CTL peptide epitope alone in vitro (ibid and continuing onto page 348). Vitiello et al further teach that antigenic peptides that bind to class I can be derived from infectious agents such as a peptide from HIV or from cancer cells, (paragraph 2 of column 1 on page 341 and reference 18 on page 349). Vitiello et al teach therapeutic vaccines comprising CTL epitopes from HBV and methods of administration in humans or in transgenic HLA-A2.1 positive animals (especially Abstract). Vitiello et al teach use of vaccines to prevent and treat infectious diseases and cancer (especially page 341 at column 2, second full paragraph).

Vitiello et al do not teach that a method of treating with therapeutic vaccines wherein a protein or polypeptide fragment thereof is altered to include an insertion of the unstable polypeptide segment recited in the instant claims.

Rogers et al teach PEST sequences are hydrophilic and acidic and contribute to the relationship between negative charge and instability, and that PEST regions confer susceptibility to rapid intracellular proteolysis. Rogers et al teach a PEST sequence RTQELEIELPSEPR that is 14 amino acid residues in length, hydrophilic, and contains less than 30% of the hydrophobic residues recited in instant claim 12.

Gilbert et al teach that unmodified soluble proteins of infectious agents do not prime MHC class I-restricted CTL responses whereas particulate proteins do prime in vivo to prevent infection (especially paragraph 1). Gilbert et al teach that Plasmodium falciparum CTL and HTL epitopes and the need to present the epitopes in a form that can prime MHC class I restricted CTL responses.

So et al teach that deaggregated protein containing CTL epitopes is highly antigenic for T cells, whereas soluble deaggregated protein is tolerizing. So et al teach that the difference in immunological properties is due to the amount of irreversibly unfolded protein in the aggregated protein composition which is extremely sensitive to protease degradation in vivo (especially last two paragraphs). So et al teach that increasing protein stability led to depression of T cell epitope generation by increasing resistance to proteolysis (especially abstract). So et al teach that controlling antigen stability to control the dose of antigenic peptide and to manipulate the resulting T cell response (especially discussion). So et al teach that proteases preferentially digest proteins in an unfolded state (especially column 1 on page 32136).

Novotny et al teach correlation among sites of limited proteolysis, enzyme accessibility and segmental mobility. Novotny et al teach limited proteolytic sites are always located at the exposed polypeptide chain segments that either connect two compact globular domains or loop out from a compact fold of a domain, and that flexibility of the polypeptide chain of a globular protein at the site of proteolytic attack promotes optimal binding and proper interaction with the active site of the protease (especially page 185).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have introduced the PEST sequence(s) taught by Rogers et al into not sufficiently immunogenic Plasmodial proteins or other unmodified soluble proteins of infectious agents taught by Gilbert et al or So et al or into the proteins or polypeptides taught by Vitiello et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to prevent or treat an infection such as taught by Gilbert et al or by Vitiello et al or to treat cancer as taught by Vitiello et al by inducing an immune response to a protein or peptide not sufficiently immunogenic, similarly to the teaching of Vitiello et al for HBV core antigen polypeptide that does not efficiently sensitize targets for lysis by CTL, by introducing a PEST sequence such as that taught by Rogers et al that is exposed and flexible and susceptible to proteolytic attack as taught by Novotny et al, especially given the teaching of Vitiello et al that the CTL epitope must be cleaved from the remainder of the polypeptide for it to associate with class I molecules and the teaching of Rogers et al that the introduction of PEST sequences introduces instability and confers susceptibility to rapid intracellular proteolysis.

With regard to the limitations recited in instant claim 1 pertaining to the unstable polypeptide segment, and those recited in instant claims 18 and 19 as pertains to the T cell epitope, to inhibit growth of neoplastic cells recited in claim 5, wherein the unstable polypeptide segment is inserted N-terminally adjacent to the T cell epitope, the limitations recited in instant claim 1 are expected properties of the unstable polypeptide segment, that the limitations recited in claims 18 and 19 are expected properties of the T cell epitope, and one of ordinary skill in the art recognized at the time the invention was made that it was an aim of inducing CTL responses to neoplastic cells to inhibit their growth. Claim 16 is included in the instant rejection because it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have located the unstable polypeptide segment terminally, including N-terminally adjacent to the T cell epitope in order to facilitate proteolytic cleavage of the said T cell epitope.

Therefore the claimed method appears to be the same or similar to the method of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the method of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

10. Claims 1-8, 10-13 and 15, 16, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vitiello et al (J. Clin. Invest. 1995 ,95: 341-349) in view of Rogers et al (Science 1986, 234(4774) : 364-368), Gilbert et al (Nature Biotechn. 1997, 15: 1280-1284), So et al (J. Biol. Chem. 1997, 272(51): 32136-32140), Novotny et al (FEB, 1987 211(2): 185-189, IDS reference) and Niedermann et al (Immunity, 1995, 2: 289-299, IDS reference).

Vitiello et al teach that most recombinant proteins and CTL peptide epitopes are poor immunogens with regard to eliciting a class I restricted CTL response, so modification by attaching a T helper peptide (HTL) epitope such as tetanus toxoid peptide 830-843 and two lipid molecules such as palmitic acid improves immunogenicity and results in long-term memory CTL induction (especially abstract and Figure 1). Vitiello et al teach that the structure of the lipopeptide is 2 molecules of palmitic acid coupled via a KSS linker, i.e., comprising a linkage of a charged amino acid residue, to the tetanus toxoid 830-843 T promiscuous, i.e, multivalent, auxiliary epitope linked via a AAA linker to HBV core 18-27 CTL peptide epitope (especially Figure 1). Vitiello et al teach that lipid modification of antigenic peptides enhances their immunogenicity (especially paragraph spanning columns 1 and 2 on page 347). Vitiello et al teach that lipid modification of peptides may help them translocate across the plasma membrane into the cytoplasm, leads to the persistence of peptides at the site of injection or in the draining lymph node for sufficient time to induce a CTL response (ibid). Vitiello et al teach that the CTL epitope must be cleaved from the remainder of the lipopeptide in order for it to associate with MHC class I molecules, and that the lipopeptide is 1000-fold less efficient in sensitizing targets for lysis by CTL than the CTL peptide epitope alone in vitro (ibid and continuing onto page 348). Vitiello et al further teach that antigenic peptides that bind to class I can be derived from infectious agents such as a peptide from HIV or from cancer cells, (paragraph 2 of column 1 on page 341 and reference 18 on page 349). Vitiello et al teach therapeutic vaccines comprising CTL epitopes from HBV and methods of administration in humans or in transgenic HLA-A2.1 positive animals (especially Abstract). Vitiello et al teach use of vaccines to prevent and treat infectious diseases and cancer (especially page 341 at column 2, second full paragraph).

Vitiello et al do not teach that a method of treating with therapeutic vaccines wherein a protein or polypeptide fragment thereof is altered to include an insertion of the unstable polypeptide segment recited in the instant claims.

Rogers et al teach PEST sequences are hydrophilic and acidic and contribute to the relationship between negative charge and instability, and that PEST regions confer susceptibility to rapid intracellular proteolysis. Rogers et al teach a PEST sequence RTQELEIELPSEPR that is 14 amino acid residues in length, hydrophilic, and contains less than 30% of the hydrophobic residues recited in instant claim 12.

Gilbert et al teach that unmodified soluble proteins of infectious agents do not prime MHC class I-restricted CTL responses whereas particulate proteins do prime in vivo to prevent infection (especially paragraph 1). Gilbert et al teach that Plasmodium falciparum CTL and HTL epitopes and the need to present the epitopes in a form that can prime MHC class I restricted CTL responses.

So et al teach that deaggregated protein containing CTL epitopes is highly antigenic for T cells, whereas soluble deaggregated protein is tolerizing. So et al teach that the difference in immunological properties is due to the amount of irreversibly unfolded protein in the aggregated protein composition which is extremely sensitive to protease degradation in vivo (especially last two paragraphs). So et al teach that increasing protein stability led to depression of T cell epitope generation by increasing resistance to proteolysis (especially abstract). So et al teach that controlling antigen stability to control the dose of antigenic peptide and to manipulate the resulting T cell response (especially discussion). So et al teach that proteases preferentially digest proteins in an unfolded state (especially column 1 on page 32136).

Novotny et al teach correlation among sites of limited proteolysis, enzyme accessibility and segmental mobility. Novotny et al teach limited proteolytic sites are always located at the exposed polypeptide chain segments that either connect two compact globular domains or loop out from a compact fold of a domain, and that flexibility of the polypeptide chain of a globular protein at the site of proteolytic attack promotes optimal binding and proper interaction with the active site of the protease (especially page 185).

Niedermann et al teach cleavage sites directly adjacent to the N- and C-terminal ends of CTL epitopes.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have introduced the PEST sequence(s) taught by Rogers et al into not sufficiently immunogenic Plasmodial proteins or other unmodified soluble proteins of infectious agents taught by Gilbert et al or So et al or into the proteins or polypeptides taught by Vitiello et al, including at the N or C termini of CTL epitopes as taught by Niederman et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to prevent or treat an infection such as taught by Gilbert et al or by Vitiello et al or to treat cancer as taught by Vitiello et al by inducing an immune response to a protein or peptide not sufficiently immunogenic, similarly to the teaching of Vitiello et al for HBV core antigen polypeptide that does not efficiently sensitize targets for lysis by CTL, by introducing a PEST sequence such as that taught by Rogers et al that is exposed and flexible and susceptible to proteolytic attack as taught by Novotny et al, especially given the teaching of Vitiello et al that the CTL epitope must be cleaved from the remainder of the polypeptide for it to associate with class I molecules and the teaching of Rogers et al that the introduction of PEST sequences introduces instability and confers susceptibility to rapid intracellular

proteolysis and the teaching of Niedermann et al that flanking residues influence proteolytic processing.

With regard to the limitations recited in instant claim 1 pertaining to the unstable polypeptide segment, and those recited in instant claims 18 and 19 as pertains to the T cell epitope, to inhibit growth of neoplastic cells recited in claim 5, wherein the unstable polypeptide segment is inserted N-terminally adjacent to the T cell epitope, the limitations recited in instant claim 1 are expected properties of the unstable polypeptide segment, that the limitations recited in claims 18 and 19 are expected properties of the T cell epitope, and one of ordinary skill in the art recognized at the time the invention was made that it was an aim of inducing CTL responses to neoplastic cells to inhibit their growth.

Therefore the claimed method appears to be the same or similar to the method of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the method of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

11. Claims 1-8, 10, 11, 13, 15, 16, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vitiello et al (J. Clin. Invest. 95, 1995 341-349) in view of Hubbard et al (Protein Science 1994, 3: 757-768, IDS reference) and Hubbard et al (J. Mol. Biol. 1991, 220: 507-530, IDS reference).

Vitiello et al teach that most recombinant proteins and CTL peptide epitopes are poor immunogens with regard to eliciting a class I restricted CTL response, so modification by attaching a T helper peptide (HTL) epitope such as tetanus toxoid peptide 830-843 and two lipid molecules such as palmitic acid improves immunogenicity and results in long-term memory CTL induction (especially abstract and Figure 1). Vitiello et al teach that the structure of the lipopeptide is 2 molecules of palmitic acid coupled via a KSS linker, i.e., comprising a linkage of a charged amino acid residue, to the tetanus toxoid 830-843 T promiscuous, i.e, multivalent, auxiliary epitope linked via a AAA linker to HBV core 18-27 CTL peptide epitope (especially Figure 1). Vitiello et al teach that lipid modification of antigenic peptides enhances their immunogenicity (especially paragraph spanning columns 1 and 2 on page 347). Vitiello et al teach that lipid modification of peptides may help them translocate across the plasma membrane into the cytoplasm, leads to the persistence of peptides at the site of injection or in the draining lymph node for sufficient time to induce a CTL response (ibid). Vitiello et al teach that the CTL epitope must be cleaved from the remainder of the lipopeptide in order for it to associate with MHC class I molecules, and that the lipopeptide is 1000-fold less efficient in sensitizing targets for lysis by CTL than the CTL peptide epitope alone in vitro (ibid and continuing onto page 348). Vitiello et al further teach that antigenic peptides that bind to class I can be derived from infectious agents such as a peptide from HIV or from cancer cells, (paragraph 2 of column 1 on page 341 and

reference 18 on page 349). Vitiello et al teach therapeutic vaccines comprising CTL epitopes from HBV and methods of administration in humans or in transgenic HLA-A2.1 positive animals (especially Abstract). Vitiello et al teach use of vaccines to prevent and treat infectious diseases and cancer (especially page 341 at column 2, second full paragraph).

Vitiello et al do not teach that a method of treating with therapeutic vaccines wherein a protein or polypeptide fragment thereof is altered to include an insertion of the unstable polypeptide segment recited in the instant claims.

Hubbard et al (Protein Science) teach that large local motions proximate to the scissile bond are required for proteolysis, and it is this ability to unfold locally without perturbing the overall protein conformation that is the prime determinant for limited proteolysis, and that at least 12 residues must be involved in the "loop" (especially abstract).

Hubbard et al (J. Mol. Biol.) teach that for limited proteolysis to occur, the protein must be capable of local unfolding without perturbation of the overall protein conformation (especially abstract). Hubbard et al further teach that at least 12 residues must be involved in the change in conformation (especially abstract) and that flexible, exposed loops would accomplish this task and that the loops comprise a protease cleavage site (especially discussion).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the flexible, exposed loops taught by Hubbard et al in the recombinant proteins or polypeptides taught by Vitiello et al and to have used the polypeptides as taught by Vitiello et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the efficiency of the immunizing peptides or polypeptides by making the epitopes susceptible to lysosomal protease cleavage in order to treat or prevent infectious disease or to treat cancer, particularly in light of the teaching of Vitiello et al that the CTL epitope must be cleaved from the remainder of the polypeptide or protein in order to bind to class I and be efficient in sensitizing targets for lysis by CTL.

With regard to the limitations recited in instant claim 1 pertaining to the unstable polypeptide segment, and those recited in instant claims 18 and 19 as pertains to the T cell epitope, to inhibit growth of neoplastic cells recited in claim 5, wherein the unstable polypeptide segment is inserted N-terminally adjacent to the T cell epitope, the limitations recited in instant claim 1 are expected properties of the unstable polypeptide segment, that the limitations recited in claims 18 and 19 are expected properties of the T cell epitope, and one of ordinary skill in the art recognized at the time the invention was made that it was an aim of inducing CTL responses to neoplastic cells to inhibit their growth. Claim 16 is included in the instant rejection because it would have been

prima facie obvious to one of ordinary skill in the art at the time the invention was made to have located the unstable polypeptide segment terminally, including N-terminally adjacent to the T cell epitope in order to facilitate proteolytic cleavage of the said T cell epitope.

Therefore the claimed method appears to be the same or similar to the method of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the method of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

12. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vitiello et al (J. Clin. Invest. 95, 1995 341-349) in view of Hubbard et al (Protein Science 1994, 3: 757-768, IDS reference) and Hubbard et al (J. Mol. Biol. 1991, 220: 507-530, IDS reference) as applied to claims 1-8, 10, 11, 13, 15, 16 and 19 supra and further in view of Rogers et al (Science 234/4774, 364-368, 1986).

Vitiello et al, Hubbard et al and Hubbard et al have been discussed supra, hereafter "the combined references".

The combined references do not teach wherein not more than 30% of the amino acid residues of the unstable polypeptide sequence are selected from the group consisting of I, L, V, Y, F, W, T and M.

Rogers et al teach PEST sequences are hydrophilic and acidic and contribute to the relationship between negative charge and instability, and that PEST regions confer susceptibility to rapid intracellular proteolysis. Rogers et al teach a PEST sequence RTQELEIELPSEPR that is 14 amino acid residues in length, hydrophilic, and contains less than 30% of the hydrophobic residues recited in instant claim 12.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the PEST sequences taught by Rogers et al in the altered protein or polypeptide taught by the combined references and to have used it in the method taught by the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to use in the method of the combined references an unstable polypeptide segment that would confer susceptibility to rapid intracellular proteolysis, such as that taught by Rogers et al.

13. Claims 1-8, 10, 11, 13, 15, 16, 18 and 19 rejected under 35 U.S.C. 103(a) as being unpatentable over Vitiello et al (J. Clin. Invest. 95, 1995 341-349) in view of Hubbard et al (Protein Science 1994, 3: 757-768, IDS reference), Hubbard et al (J. Mol. Biol. 1991, 220: 507-530, IDS reference) and Niedermann et al (Immunity, 1995, 2: 289-299, IDS reference).

Vitiello et al teach that most recombinant proteins and CTL peptide epitopes are poor immunogens with regard to eliciting a class I restricted CTL response, so modification by attaching a T helper peptide (HTL) epitope such as tetanus toxoid peptide 830-843 and two lipid molecules such as palmitic acid improves immunogenicity and results in long-term memory CTL induction (especially abstract and Figure 1). Vitiello et al teach that the structure of the lipopeptide is 2 molecules of palmitic acid coupled via a KSS linker, i.e., comprising a linkage of a charged amino acid residue, to the tetanus toxoid 830-843 T promiscuous, i.e, multivalent, auxiliary epitope linked via a AAA linker to HBV core 18-27 CTL peptide epitope (especially Figure 1). Vitiello et al teach that lipid modification of antigenic peptides enhances their immunogenicity (especially paragraph spanning columns 1 and 2 on page 347). Vitiello et al teach that lipid modification of peptides may help them translocate across the plasma membrane into the cytoplasm, leads to the persistence of peptides at the site of injection or in the draining lymph node for sufficient time to induce a CTL response (ibid). Vitiello et al teach that the CTL epitope must be cleaved from the remainder of the lipopeptide in order for it to associate with MHC class I molecules, and that the lipopeptide is 1000-fold less efficient in sensitizing targets for lysis by CTL than the CTL peptide epitope alone in vitro (ibid and continuing onto page 348). Vitiello et al further teach that antigenic peptides that bind to class I can be derived from infectious agents such as a peptide from HIV or from cancer cells, (paragraph 2 of column 1 on page 341 and reference 18 on page 349). Vitiello et al teach therapeutic vaccines comprising CTL epitopes from HBV and methods of administration in humans or in transgenic HLA-A2.1 positive animals (especially Abstract). Vitiello et al teach use of vaccines to prevent and treat infectious diseases and cancer (especially page 341 at column 2, second full paragraph).

Vitiello et al do not teach that a method of treating with therapeutic vaccines wherein a protein or polypeptide fragment thereof is altered to include an insertion of the unstable polypeptide segment recited in the instant claims.

Hubbard et al (Protein Science) teach that large local motions proximate to the scissile bond are required for proteolysis, and it is this ability to unfold locally without perturbing the overall protein conformation that is the prime determinant for limited proteolysis, and that at least 12 residues must be involved in the "loop" (especially abstract).

Hubbard et al (J. Mol. Biol.) teach that for limited proteolysis to occur, the protein must be capable of local unfolding without perturbation of the overall protein conformation (especially abstract). Hubbard et al further teach that at least 12 residues must be involved in the change in conformation (especially abstract) and that flexible, exposed loops would accomplish this task and that the loops comprise a protease cleavage site (especially discussion).

Niedermann et al teach cleavage sites directly adjacent to the N- and C-terminal ends of CTL epitopes.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the flexible, exposed loops taught by Hubbard et al in the recombinant proteins or polypeptides taught by Vitiello et al and including iat the N or C termini of CTL epitopes as taught by Niederman et al, and to have used the proteins or polypeptides as taught by Vitiello et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the efficiency of the immunizing peptides or polypeptides by making the epitopes susceptible to lysosomal protease cleavage in order to treat or prevent infectious disease or to treat cancer, particularly in light of the teaching of Vitiello et al that the CTL epitope must be cleaved from the remainder of the polypeptide or protein in order to bind to class I and be efficient in sensitizing targets for lysis by CTL and Niedermann et al teach the influence of flanking amino acid residues on proteolytic cleavage for generation of CTL epitopes.

With regard to the limitations recited in instant claim 1 pertaining to the unstable polypeptide segment, and those recited in instant claims 18 and 19 as pertains to the T cell epitope, to inhibit growth of neoplastic cells recited in claim 5, wherein the unstable polypeptide segment is inserted N-terminally adjacent to the T cell epitope, the limitations recited in instant claim 1 are expected properties of the unstable polypeptide segment, that the limitations recited in claims 18 and 19 are expected properties of the T cell epitope, and one of ordinary skill in the art recognized at the time the invention was made that it was an aim of inducing CTL responses to neoplastic cells to inhibit their growth.

Therefore the claimed method appears to be the same or similar to the method of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the method of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

14. No claim is allowed.

15. It is requested that Applicant submit a copy of the Form 1449 filed 7/13/00 as it appears to be missing from the file.

16. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Wednesday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Chan Y Christina, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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